Serum cortisol as a predictor for posttraumatic stress disorder symptoms in post-myocardial infarction patients

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Abstract: Background: After an acute myocardial infarction (MI), patients may develop posttraumatic stress disorder (PTSD). There is evidence for alterations in the hypothalamic–pituitary–adrenal axis in PTSD. An association between patients‘ cortisol level after experiencing an MI and subsequent PTSD symptoms has not been investigated yet. Therefore, the aim of this study was to examine whether serum cortisol measured in patients admitted to hospital for acute coronary care after MI is predictive of PTSD symptoms at three and 12 months post-MI, respectively. Methods: Patients (N=106) with a verified MI and high risk for the development of MI-induced PTSD symptoms were included in the study within 48 hours of hospital admission for acute coronary intervention. Serum cortisol was measured from fasting venous blood samples the next morning. Hierarchical regression analysis was used to test for an independent contribution of cortisol levels from admission to the Clinician-Administered PTSD Scale sum score three and 12 months after discharge from the coronary care unit. Result: Hierarchical regression analysis showed that lower serum cortisol levels were significantly associated with more severe PTSD symptoms three months (B=-0.002, p=0.042) and 12 months (B=-0.002, p=0.043) post-MI. Limitations: The generalizability of the findings is limited to patients with high acute peri-traumatic distress and without an acute severe depressive episode. The study does not provide any information about the diurnal cortisol pattern. Conclusion: Lower serum cortisol measured during MI hospitalization may predict more severe MI induced PTSD symptoms three and 12 months after hospital discharge.

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Serum cortisol as a predictor for posttraumatic stress disorder symptoms in post-myocardial infarction patients

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ABSTRACT

Background: After an acute myocardial infarction (MI[2]), patients may develop posttraumatic stress disorder (PTSD[3]). There is evidence for alterations in the hypothalamic–pituitary–adrenal axis in PTSD. An association between patients` cortisol level after experiencing an MI and subsequent PTSD symptoms has not been investigated yet. Therefore, the aim of this study was to examine whether serum cortisol measured in patients admitted to hospital for acute coronary care after MI is predictive of PTSD symptoms at three and 12 months post-MI, respectively.

Methods: Patients (N=106) with a verified MI and high risk for the development of MI-induced PTSD symptoms were included in the study within 48 hours of hospital admission for acute coronary intervention. Serum cortisol was measured from fasting venous blood samples the next morning. Hierarchical regression analysis was used to test for an independent contribution of cortisol levels from admission to the Clinician-Administered PTSD Scale sum score three and 12 months after discharge from the coronary care unit.

Results: Hierarchical regression analysis showed that lower serum cortisol levels were significantly associated with more severe PTSD symptoms three months (B=-0.002, p=0.042) and 12 months (B=-0.002, p=0.043) post-MI.

Limitations: The generalizability of the findings is limited to patients with high acute peri-traumatic distress and without an acute severe depressive episode. The study does not provide any information about the diurnal cortisol pattern.

Conclusion: Lower serum cortisol measured during MI hospitalization may predict more severe MI-induced PTSD symptoms three and 12 months after hospital discharge.

Introduction

In 2015, an estimated 7.28 million acute myocardial infarctions (MI) occurred globally (Roth et al., 2017). MI is a life-threatening event, and patients may therefore experience high distress and fear of dying (Whitehead et al., 2005). In the aftermath of MI, patients may develop

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[2] MI: myocardial infarction
[3] PTSD: posttraumatic stress disorder

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substantial psychological symptoms, including posttraumatic stress disorder (PTSD) (Vilchinsky et al., 2017). After experiencing an acute coronary syndrome (ACS), approximately 12% of patients show clinically significant PTSD symptoms and around 4% are diagnosed with PTSD (Edmondson et al., 2012). Patients with MI-induced PTSD symptoms may re-experience the event in the form of intermittent distressing thoughts or nightmares. They may avoid reminders of the MI such as certain places or activities and may also have problems in concentrating or sleeping because of elevated arousal. In addition to impairing patients' mental health and daily functioning, MI-triggered PTSD symptoms have also been associated with an increased risk of hospital readmission due to cardiovascular disease events (Edmondson et al., 2011; Shemesh et al., 2004; Tsutsui et al., 2017; von Känel et al., 2011) and all-cause mortality (Edmondson et al., 2011; Tsutsui et al., 2017).

Cortisol is a hormone secreted by the adrenals with an important role in stress response. Several studies have investigated possible alterations in the hypothalamic–pituitary–adrenal (HPA) axis in PTSD, but findings regarding cortisol levels are inconsistent as reported by different meta-analyses. For example, morning salivary cortisol levels were lower in patients with PTSD compared to non-trauma-exposed (NE) controls and mentally healthy trauma-exposed patients (TE) (Pan et al., 2018). Another meta-analysis found lower morning cortisol and lower 24 hours cortisol in patients with PTSD compared to controls consisting of NE, TE and patients with unknown trauma-exposure (Schumacher et al., 2019). In contrast, there was no difference in cortisol levels between TE and PTSD patients with adulthood trauma, and furthermore no difference was found between TE and NE (Klaassens et al., 2012). In another study, cortisol levels were found to be lower in PTSD patients than in NE, but there was no difference between PTSD patients and TE (Meewisse et al., 2007). Inclusion of patients with ACS-induced PTSD symptoms was not reported in any of these meta-analyses (Klaassens et al., 2012; Meewisse et al., 2007; Pan et al., 2018; Schumacher et al., 2019). One previous study showed an inverse correlation between plasma cortisol and PTSD symptoms 18-44 months after MI, after adjusting for depressive symptoms (von Känel et al., 2010).

In addition to studies on cortisol levels in patients with diagnosed PTSD, there are also studies on the prognostic value of cortisol levels measured shortly after the traumatic event (Bonne et al., 2003; Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011; Mouthaan et al., 2014; Shalev et al., 2008). Some of these studies suggest that a lower cortisol level, measured in the close aftermath of a traumatic event, might be associated with the development of PTSD and PTSD symptoms (Delahanty et al., 2000; Ehring et al., 2008; McFarlane et al., 2011; Mouthaan et al., 2014). For example, lowered plasma cortisol levels measured in the trauma resuscitation room were predictive of acute and chronic PTSD symptoms (Mouthaan et al., 2014). This is in line with other studies showing an association between lower cortisol levels measured shortly after the experience of a traumatic event and subsequent PTSD symptoms (Ehring et al., 2008; McFarlane et al., 2011) and PTSD diagnosis (Delahanty et al., 2000). Yet, there are also studies which reported a lack of association between the initial cortisol level and PTSD symptoms at follow-up (Bonne et al., 2003) and PTSD diagnosis in civilian trauma victims (Shalev et al., 2008).

Decreased cortisol may play a role in the development of PTSD symptoms (Yehuda, 2002a), further evidenced by studies showing that hydrocortisone given shortly after experiencing a traumatic event might prevent the development of PTSD (Schelling et al., 2001) and PTSD symptoms (Delahanty et al., 2013).

Whether cortisol levels measured shortly after MI are predictive of subsequent MI-triggered PTSD symptoms has not been investigated yet. A predictive laboratory marker would be valuable because it might allow the early identification of patients at an increased risk of developing post-MI PTSD symptoms. Based on this knowledge early preventive strategies could potentially be implemented. Therefore, the aim of this study was to investigate whether serum cortisol levels at hospitalization for MI are predictive of PTSD symptoms 1) three months and 2) 12 months after hospitalization for acute coronary intervention for MI.

Methods

Participants

Participants in the current study were from the Myocardial Infarction – Stress Prevention Intervention (MI-SPRINT) trial that took place between January 8, 2013 and December 15, 2015 at the Bern University Hospital (Meister et al., 2013; von Känel et al., 2018). The aim of this randomized, controlled trial (RCT) was to investigate whether an early psychological trauma-focused counselling session had a preventive effect on the development of PTSD following acute MI in a high-risk population (Meister et al., 2013; von Känel et al., 2018). The ethics committee of the State of Bern approved the research protocol (KEK No. 170/12). Written informed consent to participate in the study was obtained from all patients included in this RCT.

Participants of this study were patients aged 18 years or older with either an acute ST elevation myocardial infarction (STEMI) or a non-STEMI, stable circulatory conditions, and a high risk for the development of an MI-triggered PTSD, admitted to the coronary care unit (CCU) of the Cardiology Department at the Bern University Hospital. Risk for MI-induced PTSD was evaluated with three questions assessing acute peri-traumatic distress on a numeric rating scale from 0-10: a) chest pain while suffering MI, b) fear of dying until being admitted to the CCU and c) feeling of helplessness when confronted with the diagnosis of MI. In order to be classified as a high-risk patient, the extent of chest pain had to have a score of at least 5 together with a score of at least 5 for fear of dying and/or feeling of helplessness.

Exclusion criteria were insufficient language proficiency in German, participation in another RCT, emergency coronary artery bypass graft surgery, a current severe depressive episode or another comorbid disease with an estimated life expectancy under one year in patient's medical history, suicidal ideation in the last two weeks, and lack of orientation with regard to situation, place and person.

Intervention

Psychological counselling sessions carried out as part of the MI-SPRINT trial are described in detail elsewhere (Meister et al., 2013; von Känel et al., 2018). In brief, counselling was given by study therapists (i.e., doctoral students in psychology or medicine) within 48 hours after admission to the CCU. The verum group was given trauma-focused counselling consisting of extensive information about the development, symptomatology and treatment of PTSD and the concept of an MI as a traumatic experience. The control group was given information on the general role of psychological stress in cardiovascular disease and psychological stress management tools. The duration of each counselling session was 45 minutes. In both groups, participants received an information booklet illustrating the content of the respective counselling session.

Measurements

Measurements were carried out at three different time points (Fig. 1): 1. within 48 hours of hospitalization, when patients had reached stable circulatory condition, with one single blood sample the next morning after the counselling session took place (admission); 2. three months after discharge from the CCU (three-month follow-up) and 3. 12 months after discharge from the CCU (12-month follow-up).

Posttraumatic stress

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), PTSD is characterized by four different symptom clusters (i.e., intrusion,

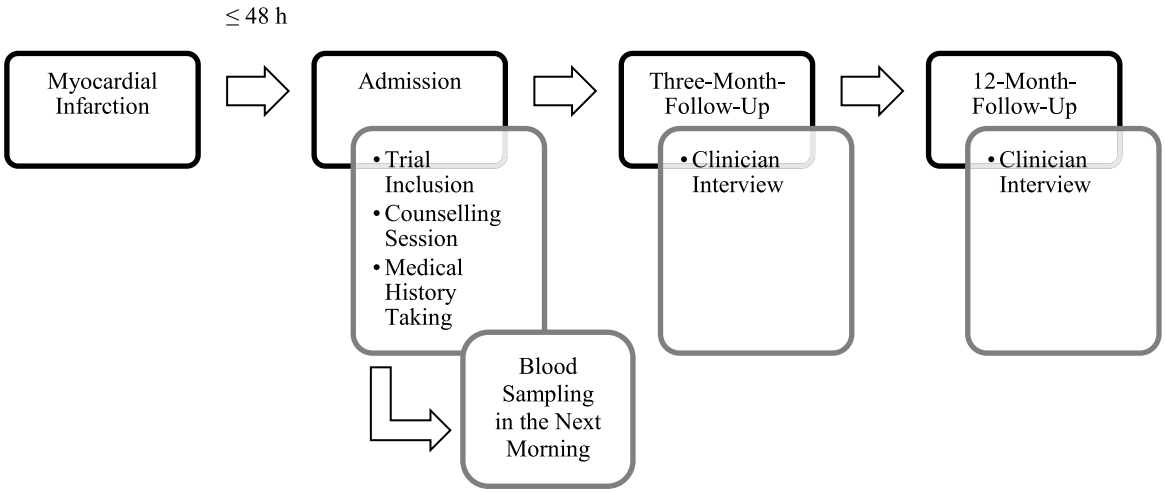

Fig. 1. Illustration of the different study time points.

avoidance, negative alterations in cognitions and mood and alterations in arousal and reactivity) which may occur after experiencing a traumatic event. For a diagnosis of PTSD to be made, the duration of symptoms must be at least one month and there must be clinically relevant distress or impaired daily functioning (American Psychiatric Association, 2013).

To evaluate posttraumatic stress, we used the validated German version (Schnyder and Moergeli, 2002) of the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). CAPS refers to the PTSD criteria of DSM-IV (American Psychiatric Association, 1994) since the MI-SPRINT trial was planned before the introduction of DSM-5.

Seventeen possible symptoms of PTSD are looked for which belong to one of the three symptom clusters of re-experiencing, avoidance/numbing or hyperarousal. For each symptom, frequency and intensity between 0 (=never) and 4 (=almost always) were assessed. For a symptom to be present, the frequency needs to have at least a value of 1 and the intensity a value of at least 2. CAPS sum score can range from 0 to 136. In this study, the CAPS sum scores recorded at three-month and 12-month follow-up were included as outcome variables in the hierarchical regression analysis. In this sample, Cronbach's α for the CAPS sum score was 0.81 at three-month follow-up and 0.71 at 12 months, indicating good and acceptable internal consistency, respectively.

Cortisol

Cortisol (nmol/L) was measured in fasting venous blood samples taken at 6 am, the morning after the counselling session had taken place. For reasons of logistics or patient care, there were deviations in the measuring time in certain cases (n=36). Specific collection times were between midnight and 6 am (n=19), at 6 am (n=68), between 6 am and 8 am (n=6) and between 11 am and 6 pm (n=10). For the same reasons as mentioned above, non-fasting blood samples were taken from six participants. The serum cortisol samples were analyzed by an electrochemiluminescence immunoassay on a Cobas analyzer (Roche Diagnostics, Switzerland). All measurements were carried out by an accredited laboratory (Institute of Clinical Chemistry, Bern University Hospital).

Methods

Covariates were selected a priori based on a literature search and theoretical considerations.

Sociodemographic factors

Information on age and gender was obtained from patients' hospital charts. Patients were asked about their highest level of education by the study therapist at admission. A distinction was made between four different levels of education: 1: lower than apprenticeship or vocational school; 2: apprenticeship or vocational school; 3: high school graduation; 4: university graduation, including applied sciences (Bopp et al., 2003).

Medical history

At admission, patients were asked whether they had ever suffered from depression in the past. To assess previous posttraumatic experiences in patients' lives with possible PTSD symptoms in the last three months before the MI-hospitalization, three questions from the Structured Clinical Interview for DSM-IV-PTSD (Wittchen and Fydrich, 1997) were asked at admission. Information was obtained from patients on experience of traumatic events before being admitted to hospital for acute coronary treatment for MI and if any, whether there had been moments of re-experiencing such events in nightmares, flashbacks or thoughts and if these moments had occurred in the last three months before hospitalization for MI. It has been shown that three "yes" answers to these questions correctly diagnosed 97% of PTSD cases (Franklin et al., 2002).

The German version of the four-item Jenkins Sleep Questionnaire (Jenkins et al., 1988) was used to evaluate the subjective sleep quality in four weeks prior to hospitalization for MI. Participants were asked about a) difficulties falling asleep; b) waking up at night; c) waking up at night with troubles falling asleep again and d) feeling tired after an usual amount of sleep. Response options were: 0: not at all; 1: 1–3 days; 2: 4–7 days; 3: 8–14 days; 4: 15–21 days and 5: 22–28 days. For the analysis, the mean score of the four items (between 0 and 5) was calculated.

Objective indices of the MI severity

For evaluating the severity of MI, the Global Registry of Acute Coronary Event (GRACE) risk score was used (Fox et al., 2006). The GRACE risk score predicts the risk of death or MI within six months after admission for an ACS (Fox et al., 2006). The score includes the following variables: age, heart rate, systolic blood pressure, serum creatinine, elevated cardiac enzymes, Killip class, cardiac arrest and ST-segment deviation at admission (Fox et al., 2006). Another variable used to objectify the severity of the MI was the need for resuscitation at hospitalization (by cardioversion or mechanical).

Intervention

Since the MI-SPRINT trial aimed to investigate whether a trauma-focused counselling session prevents the development of an MI-induced PTSD, the type of intervention was also taken into account.

Statistical analysis

For the statistical analysis, IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY) was used. The significance level was set at $p<0.05$ (two-tailed). Due to a number of missing values for the 12-month follow-up, we analyzed only the data of participants who completed the CAPS after 12 months (N=106) (Fig. 2). The CAPS sum

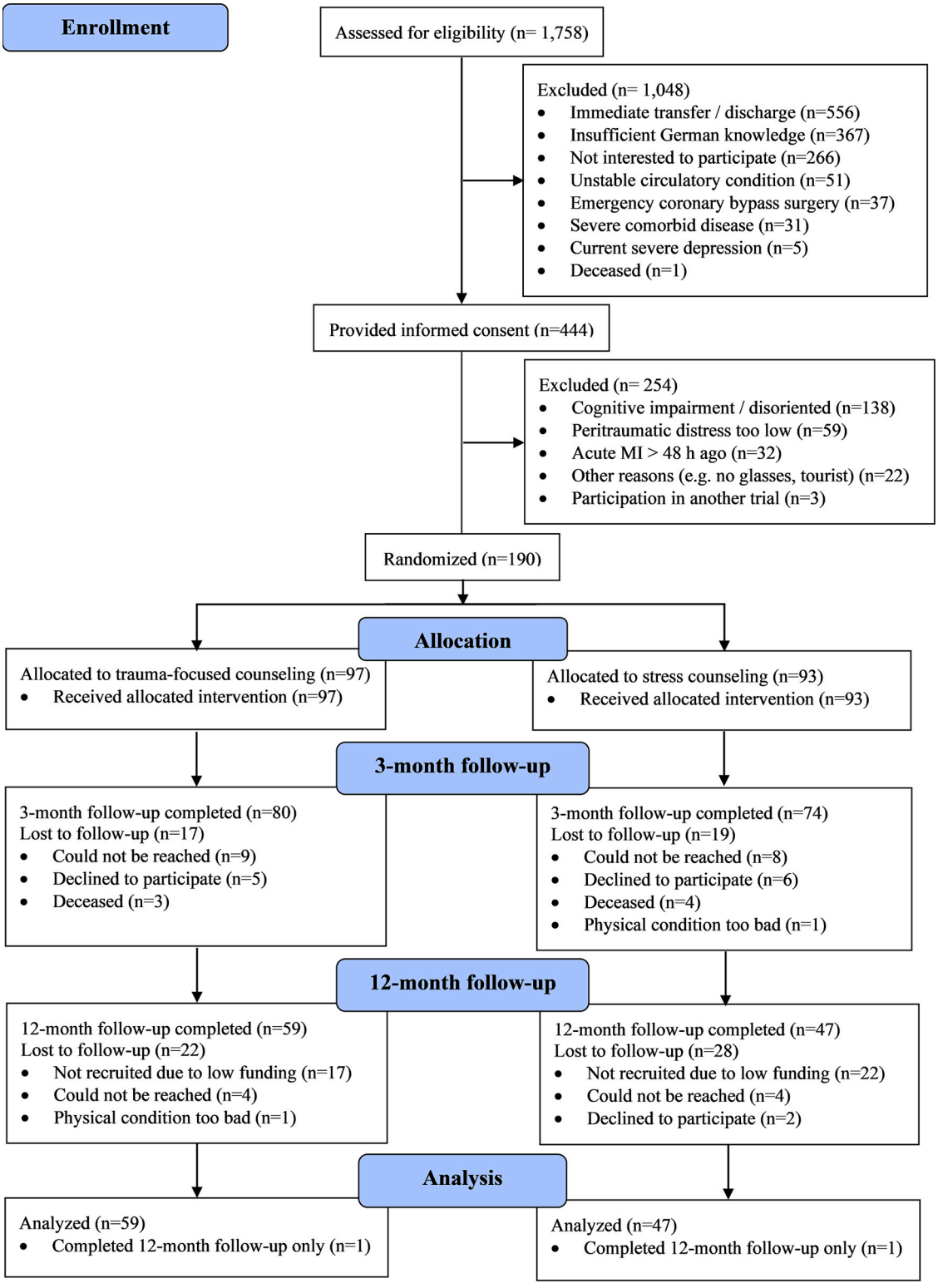

Fig. 2. Flow diagram for the included study participants (N=106).

score at the three-month follow-up was not assessed in two of these 106 subjects. Cortisol values at admission were missing in three cases. Information about the highest level of education, history of depression and about sleep quality were missing in one case each. The GRACE risk score was not calculated for five patients. In eight participants, there was no information about PTSD in the past. All these missing values were replaced by the expectation maximization algorithm (EM).

Normal distribution was tested with the Kolmogorov-Smirnov test. Group differences in cortisol levels were calculated using Student's t-test and analysis of variance (ANOVA).

To approximate a normal distribution, CAPS sum scores from the three- and 12-month follow-up were square root transformed for the hierarchical regression analysis. Hierarchical regression analysis with the stepwise method was used to test for an independent contribution of cortisol levels at admission to the CAPS sum score of the three- and 12-month follow-up. We defined the CAPS sum score of the three-month follow-up and of the 12-month follow-up as the dependent variable in two separate regression models. We added the variables to the model in three blocks. In a first step, we entered demographic variables (age and sex), the highest level of education and the variable intervention (i.e., trauma-focused or stress-focused counselling session). The second block consisted of objective indices of severity of MI (i.e., GRACE risk score and need of resuscitation), variables of the medical history (i.e., history of depression, history of PTSD and sleep quality). Cortisol levels measured at admission were entered in the third step. Linearity and homoscedasticity were approved by means of scatter plots. Exclusion of autocorrelation was done by interpreting Durbin Watson statistics. We used variance inflation factor to check for the absence of multicollinearity. Cook's distance gave no concern of influential outliers.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. All patients were of Caucasian ethnicity. Patients were predominantly male (83%), had a STEMI (69.8%) and had mid-to-high educational level; 25.5% had a history of depression.

Cortisol

Mean cortisol was 492.52 nmol/L (SD: 181.85). Cortisol was normal distributed (p=0.096). Neither specific collection time (all p-values>0.05) nor fasting state (p=0.90) were associated with serum cortisol levels. Likewise, the intake of glucocorticoids (n=3) was not associated with cortisol levels (p=0.62).

Hierarchical regression analysis for CAPS sum score at three-month follow-up

Table 2 shows the results for the hierarchical regression analysis with the three models (1a-c). In model 1a, none of the entered variables was significantly associated with the CAPS sum score. In model 1b, the variable sleep quality (i.e., the mean score of the Jenkins Sleep Questionnaire) significantly contributed to the outcome (B=0.392, p=0.004). In model 1c, age (B=-0.043, p=0.040), level of education (B=-0.393, p=0.037) and again sleep quality (B=0.418, p=0.002) were significantly related to the outcome. Additionally, cortisol levels were significantly and inversely associated with the CAPS sum score (B=-0.002, p=0.042). Cortisol explained 3.5% of the total variance after taking all covariates into account. The model explained 14.8% of the variance in the CAPS sum score.

Table 1
Characteristics of Study Participants (N=106)

Characteristics	Mean ± Standard Deviation	n (%)
Age, years	59.7±9.9	
Male gender		88 (83)
Intervention, verum		59 (55.7)
Intervention, control		47 (44.3)
Highest level of education: lower than apprenticeship or vocational school		11 (10.4)
Highest level of education: apprenticeship or vocational school		76 (71.7)
Highest level of education: high school graduation		3 (2.8)
Highest level of education: university graduation, including applied sciences		16 (15.1)
STEMI		74 (69.8)
Non-STEMI		32 (30.2)
GRACE score	104.2±25.8	
Need for resuscitation		7 (6.6)
Need for resuscitation, cardioversion		7 (6.6)
Need for resuscitation, mechanical		0 (0)
History of depression		27 (25.5)
History of PTSD		7 (6.6)
Mean score in the Jenkins Sleep Questionnaire	1.49±1.22	
CAPS sum score, 3-month follow-up	11.34±11.22	
CAPS sum score, 12-month follow-up	9.44±8.67	
Cortisol, nmol/L	492.52±181.85	

Verum, study group with trauma-focused counselling; Control, study group with psychological stress counselling; STEMI, ST-Elevation Myocardial Infarction; GRACE, Global Registry of Acute Coronary Events; PTSD, posttraumatic stress disorder; CAPS, Clinician-Administered PTSD Scale. Continuous variables are given as mean values with standard deviation.

Hierarchical regression analysis for CAPS sum score at 12-month follow-up

Table 3 summarizes the results of the hierarchical regression analysis with the three models (1a-c). Only gender was significantly associated with the outcome variable in model 1a. Women scored significantly higher on the CAPS sum score than men (B=0.780, p=0.040). In model 1b, the variable intervention (B=-0.688, p=0.018), history of depression (B=0.883, p=0.009) and sleep quality (B=0.232, p=0.049) significantly contributed to the CAPS sum score of 12-month follow-up. Participants from the verum group (i.e., those with a trauma-focused counselling session) showed significantly higher posttraumatic stress symptoms at 12 months after MI than those in the control group. Patients who had a history of depression had significantly higher CAPS sum scores than those without a history of depression. In the final model (1c) age (B=-0.040, p=0.029), intervention (B=-0.713, p=0.013), history of depression (B=0.980, p=0.004) and sleep quality (B=0.255, p=0.029) were significantly related with the outcome. Again, participants in the verum group and those with a history of depression showed a higher CAPS sum score. Cortisol was an independent predictor for the CAPS sum score in the final model 1c (B=-0.002, p=0.043), explaining 3.2% of the total variance of the CAPS sum score from 12-month follow-up after taking all covariates into account. The final model explained 20% of the variance in the CAPS sum score at 12 months.

Discussion

We found that serum cortisol levels measured in the close aftermath of MI were inversely and significantly associated with MI-induced PTSD symptoms measured three and 12 months later in patients at high-risk to develop PTSD. The total variance of the CAPS sum score explained by the final model in both hierarchical regression analyses was rather

Table 2
Hierarchical regression analysis with the Clinician-Administered PTSD Scale sum score at three-month follow-up as outcome variable

Statistics of the Entire Model	Entered Variables	B	S.E.	β	p	r^2
Model 1a ($F_{4, 101}$=1.378, p=0.247, adjusted R^2=0.014)	Gender	0.169	0.428	0.038	0.695	0.001
	Age	-0.022	0.016	-0.130	0.183	0.017
	Education level	-0.364	0.197	-0.182	0.068	0.032
	Intervention	-0.283	0.329	-0.085	0.391	0.007
Model 1b ($F_{9, 96}$=2.577, p=0.011, adjusted R^2=0.119)	Gender	-0.142	0.453	-0.032	0.744	0.001
	Age	-0.037	0.021	-0.221	0.078	0.027
	Education level	-0.356	0.188	-0.178	0.061	0.030
	Intervention	-0.409	0.324	-0.123	0.211	0.013
	GRACE score	0.009	0.008	0.141	0.265	0.011
	Need for resuscitation	-0.183	0.636	-0.027	0.774	0.001
	History of depression	0.604	0.378	0.159	0.113	0.021
	History of PTSD	-0.279	0.643	-0.042	0.666	0.002
	Sleep quality	0.392	0.132	0.286	**0.004**	0.073
Model 1c ($F_{10, 95}$=2.823, p=0.004, adjusted R^2=0.148)	Gender	-0.337	0.438	-0.076	0.443	0.005
	Age	-0.043	0.021	-0.256	**0.040**	0.035
	Education level	-0.393	0.186	-0.196	**0.037**	0.037
	Intervention	-0.437	0.319	-0.131	0.174	0.015
	GRACE score	0.011	0.008	0.177	0.159	0.016
	Need for resuscitation	-0.361	0.631	-0.054	0.569	0.003
	History of depression	0.715	0.376	0.188	0.060	0.029
	History of PTSD	-0.589	0.650	-0.088	0.367	0.007
	Sleep quality	0.418	0.131	0.305	**0.002**	0.083
	Cortisol	-0.002	0.001	-0.203	**0.042**	0.035

GRACE, Global Registry of Acute Coronary Events; PTSD, posttraumatic stress disorder. Data are given as unstandardized coefficient B with Standard Error (S.E.) and β, standardized β coefficient; predictor variables were entered in three blocks (models a-c).

Table 3
Hierarchical regression analysis with the Clinician-Administered PTSD Scale sum score of 12-month follow-up as outcome variable

Statistics of the Entire Model	Entered Variables	B	S.E.	β	p	r^2
Model 1a ($F_{4, 101}$=3.112, p=0.018, adjusted R^2=0.074)	Gender	0.780	0.375	0.196	**0.040**	0.038
	Age	-0.030	0.014	-0.199	**0.036**	0.040
	Education level	-0.105	0.173	-0.058	0.545	0.003
	Intervention	-0.515	0.288	-0.171	0.077	0.028
Model 1b ($F_{9, 96}$=3.357, p=0.001, adjusted R^2=0.168)	Gender	0.435	0.382	0.109	0.258	0.010
	Age	-0.035	0.018	-0.231	0.058	0.029
	Education level	-0.118	0.165	-0.065	0.478	0.004
	Intervention	-0.688	0.285	-0.228	**0.018**	0.046
	GRACE score	0.003	0.007	0.052	0.671	0.001
	Need for resuscitation	0.613	0.559	0.102	0.275	0.010
	History of depression	0.883	0.332	0.257	**0.009**	0.056
	History of PTSD	0.160	0.565	0.026	0.778	0.001
	Sleep quality	0.232	0.116	0.188	**0.049**	0.032
Model 1c ($F_{10, 95}$=3.545, p=0.001, adjusted R^2=0.195)	Gender	0.264	0.385	0.066	0.494	0.004
	Age	-0.040	0.018	-0.265	**0.029**	0.038
	Education level	-0.150	0.163	-0.083	0.361	0.006
	Intervention	-0.713	0.281	-0.236	**0.013**	0.049
	GRACE score	0.005	0.007	0.087	0.474	0.004
	Need for resuscitation	0.458	0.555	0.076	0.411	0.005
	History of depression	0.980	0.330	0.285	**0.004**	0.068
	History of PTSD	-0.112	0.571	-0.019	0.844	0.000
	Sleep quality	0.255	0.115	0.206	**0.029**	0.038
	Cortisol	-0.002	0.001	-0.197	**0.043**	0.032

GRACE, Global Registry of Acute Coronary Events; PTSD, posttraumatic stress disorder. Data are given as unstandardized coefficient B with Standard Error (S.E.) and β, standardized β coefficient; predictor variables were entered in three blocks (models a-c).

modest; furthermore, the independent contribution of cortisol to the CAPS sum scores three- and 12-months post-MI was also small. Nevertheless, this finding is a novelty in patients with ACS-induced PTSD symptoms and it concurs with observations in non-ACS populations.

Lower plasma cortisol in patients exposed to trauma at initial medical examination was predictive of PTSD symptoms six weeks and six months later, controlling for age, gender, injury, admission to intensive care unit, time of blood collection and trauma history (Mouthaan et al., 2014). Another study found lower salivary cortisol measured in the emergency room being predictive of higher PTSD symptom severity in motor vehicle accident survivors (Ehring et al., 2008). Similarly, salivary morning cortisol measured two days after hospital admission correlated inversely with PTSD symptoms six months later in patients with a traumatic accident (McFarlane et al., 2011).

A possible explanation of why decreased cortisol levels may facilitate the development of PTSD symptoms is through a reduced down-regulation of the sympathetic nervous system (SNS) (Yehuda, 2002b; Yehuda and LeDoux, 2007), which is known to have a regulatory role in memory consolidation (McGaugh and Roozendaal, 2002). The reduced SNS containment due to decreased cortisol might lead to a stronger memory consolidation of the traumatic event resulting in intense distress feelings; these feelings might alter the perception of the trauma and therefore may delay further recovery (Yehuda, 2002b).

Another theory of the memory-regulating role of glucocorticoids is that they may enhance memory consolidation of emotionally arousing experiences but later on also reduce memory retrieval after initial consolidation (de Quervain et al., 2009).

Moreover, there is evidence that hydrocortisone given after a traumatic event reduces the risk for the development of PTSD in patients with septic shock (Schelling et al., 2001) and of PTSD symptoms in patients with traumatic injury (Delahanty et al., 2013) or cardiac surgery (Schelling et al., 2004; Weis et al., 2006). Furthermore, a meta-analysis found hydrocortisone as being potentially effective in the prevention of PTSD development in adults with severe physical illness or injury (Astill Wright et al., 2019). Whether this is also a preventive option in the case of MI-induced PTSD has, to the best of our knowledge, not been investigated yet. Outcome after corticosteroid therapy in MI patients is worth investigating further. According to a systematic meta-analysis, treatment of MI patients with corticosteroids is not harmful (Giugliano et al., 2003)

As MI-related PTSD symptoms are known to be associated with poorer cardiovascular outcome (Edmondson et al., 2011; Shemesh et al., 2004; Tsutsui et al., 2017; von Känel et al., 2011), it is highly desirable to have a preventive strategy at hand. Any reduction in MI-related PTSD would contribute not only to improved mental health, but also to a better cardiovascular outcome. As yet, this is only a theoretical assumption and further studies on serum cortisol levels in post-MI patients with PTSD symptoms are needed. It would also be useful to have a defined cortisol cut-off value that indicates a higher risk of developing PTSD, a task for future research.

Limitations

There are several limitations to this study. This study is a secondary data analysis of the MI-SPRINT RCT. The RCT was primarily designed to test a different hypothesis than the one tested in this study. It should be kept in mind that all participants got counselling. The generalizability of our findings is limited as the MI-SPRINT RCT included patients with

high acute peri-traumatic distress and without an acute severe depressive episode. Furthermore, we sampled serum cortisol only once and collected no serial measurements with short intervals which would have yielded more reliable cortisol values given the pulsatile release of cortisol. Additionally, our study does not provide any information about the diurnal cortisol pattern, including awakening response and slope.

Moreover, a receiver operating characteristic curve would have been interesting to define a cortisol cut-off value that is associated with the development of a subsequent PTSD. However, this analysis was not possible in our study population as there was only one patient who fulfilled the criteria for a DSM-IV diagnosis of PTSD.

Finally, our study did not consider depressive and anxiety symptoms. It is known that post-MI patients are at high risk of depressive or anxiety disorders (Feng et al., 2016). Possible changes in the HPA-axis activity in patients with depression (Malhi and Mann, 2018) or anxiety disorder (Vreeburg et al., 2010) have been reported, so future studies should take this into account.

Conclusion

Taken together, the findings of this study suggest that lower serum cortisol levels measured during MI hospitalization are associated with more severe PTSD symptoms in post-MI patients three and 12 months after discharge from the CCU. These results may have implications for early identification of patients suffering from MI who are at risk for the development of MI-induced PTSD symptoms. Cortisol levels can easily be measured in the clinical setting and therefore, further investigation of cortisol levels in patients with MI-induced PTSD symptoms seems worthwhile. Future studies need to identify a cortisol cut-off value defining patients at high risk for MI-induced PTSD symptoms. In addition, the findings of the present study suggest that investigation of patients' cortisol levels as a possible target for intervention to prevent ACS-induced PTSD is warranted.

Author contribution

Authors RvK, JPS, US, HZ and JB designed the MI-SPRINT trial and wrote the protocol. NS and MP designed the concept for the secondary data analysis for this study. REML and MP contributed to the acquisition of the data. Author NS managed the literature searches and analyses. Author NS undertook the statistical analysis, and author NS wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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